Chronic migraine and medication overuse: Still a debate

Abouch Valenty Krymchantowski, MD, MSc, PhD, FAHS

Diretor e Fundador do Centro de Avaliação e Tratamento da Dor de Cabeça do Rio de Janeiro; Coordenador do Ambulatório de Cefaléias Crônicas do Instituto de Neurologia Deolindo Couto da UFRJ; Membro das Sociedades Brasileira, Americana e Internacional de Cefaléia

Progressive headache consequent to drug overuse is an old critical issue. Migraine specially and the development of its daily or near-daily presentation due to overuse of immediate-relief medications is suggested since the eighties when Mathew and col. described this transformation and named it transformed migraine. These authors called the attention for the fact that migraine may progressively transform into daily headache and lose its typical clinical features under the influence of analgesic overuse. Almost simultaneously, Kudrow demonstrated an improvement in attack frequency in those patients able to withdraw from this pattern of drug consumption. Even before that, ergotamine tartrate was associated with dependence and withdrawal headaches introducing the term rebound and postulating that all ergots could promote increasing of headache frequency. Other researchers and clinicians have been demonstrating that migraineurs may develop daily or near-daily headache when using excessively caffeine, opioids, triptans and analgesics, even for purposes other than headache, and that improvement in the frequency of headache attacks occurs following abrupt discontinuation with the patients restoring the initial episodic presentation of their head pain.

Despite chronic daily headache and chronic or transformed migraine patients do overuse symptomatic medications in a frequent manner, the debate concerning whether this pattern of overuse is responsible for the frequency evolution or migraine itself is a progressive and relapsing neurologic disorder, that will turn into daily or near-daily headache as part of a natural history disease evolution, remains unresolved and a matter of disputing. Concepts in favor of a consequence rather than a cause recall the absence of true placebo-controlled trials proving the existence of headache due to drug rebound (with the honorable exception of Silverman’s trial on caffeine). In addition, there is still doubt whether rebound headache occurs from repeated episodes of withdrawal (mini-withdrawals) or the process of transformation involves a pro-nociceptive effect of symptomatic medications overuse in this population of patients. Moreover, population-based studies have been showing that only one third of chronic or transformed migraineurs overuse medications for acute treatment despite of the observations in specific clinic-based studies demonstrating that over 80% of chronic migraine patients do take analgesics on a daily or near-daily basis. Another point of interest in this debate is the fact that long-term prognosis for those that were able to withdraw did not reveal a significant improvement in order to support the suggestion emphasizing the medication overuse as the sole cause for migraine transformation. Furthermore, behavioral and psychological disturbances such anxiety, depression and nervousness as well as drug abuse profile are frequently encountered in chronic migraineurs. It is uncertain whether these alterations have a causative role in this pattern transformation or represent a consequence of years of suffering.

In addition, migraine may be a chronically progressive disorder with a clinical presentation reflecting inexorable changes in central nociceptive and pain modulatory systems that will end up resulting in neuronal sensitization and impaired descending inhibitory control of trigeminal caudalis neurons. The consequence for these possibly involved mechanisms may lead to facilitation of ascending trigeminal nociceptive pathways and the increasingly frequency of attacks, along with persistent pain, could result in use of symptomatic medications on a daily or near-daily basis. In
this subject, there has to be emphasized that the presence of peripheral nociceptors spontaneously active provokes excessive stimuli on second-order neurons in spinal cord. These, too, may become spontaneously active, induce a state of hyperexcitability that will develop constant response even to mild stimuli.11

Therefore, transformed or chronic migraine may be rather than a consequence of excessive intake of acute medications, a relapsing and progressive disorder associated with physiologic and structural changes within the brain resulting in chronic and continuous pain.

However, there is abundant clinical evidence supporting that the regular or frequent use of symptomatic medications can perpetuate and even induce, in some patients, the pattern of daily or near-daily headache. The phenomenon of opioid analgesic tolerance and the development paradoxical pain after prolonged administration of these substances is well documented as well.15 Moreover, comparing the evolution of patients with episodic migraine and those without it that were submitted to the continuous use of analgesics for other purposes than headache, one corroborates the need for the past presence of such disorder in order to achieve transformation into the chronic presentation, which means that episodic migraine is a prerequisite for the development of daily headache from symptomatic medication overuse. In addition, the preventative treatment of migraine doesn’t seem to provide frequency amelioration when the patient remains under the influence of symptomatic medication overuse.11

Despite the uncertainty of whether daily headache and medication-induced headache coexist as simultaneous disorders or have causal relationship, the need for eliminating the medication overuse should be a priority and appears to embrace a consensus among researchers and clinicians. Complete withdrawal from headache medication is the treatment of choice for patients with chronic migraine overusing these substances.16 However, the main obstacle for stopping the overused medications is the headache escalation and withdrawal symptoms. Nausea, vomiting, nervousness, sleep disturbances and even seizures may be present and challenge the efforts to keep the patients out of such pattern of drug consumption. The headache worsening along with the withdrawal symptoms may last for up to 10 days (even longer) and typically, the intensity of withdrawal headache increases between the second and fourth days.17,18 Some of the patients cannot tolerate these symptoms along with the headache exacerbation and require hospitalization and the parenteral administration of dihydroergotamine, neuroleptics and steroids.19,20,21 Others return almost immediately to the profile of excessive drug consumption. Replacement therapy with substances such as dihydroergotamine, sumatriptan, naproxen and prednisone for several days has been advocated19,22-25 while others simply recommend no medication at all during the first days of withdrawal, in order to reverse previously learned illness behavior.26 After the initial withdrawal period most of the patients not overusing opioids will adhere to the treatment, even on an outpatient basis, and present a decrease in headache frequency.27

However, the common assumed diagnosis of medication-induced headache in all of these patients is misguided. Although many will experience a short-term withdrawal syndrome characterized by worsening headache and abstinence symptoms followed by marked improvement of frequency and sometimes clear-cut restoration of the episodic headache presentation, a significant proportion of these patients will continue to experience long-term disability due to frequent headache attacks. The lines of research are not convergent at this time and both sides have fundament for their viewpoints. However, until more is proven, the efforts for a closer collaboration between defendants of both concepts will certainly improve the perspectives of knowledge in this field and certainly raise expectations for a better life for these patients.

REFERENCES

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